PATENT
Attorney Docket No. 054160-5060

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of: **Tsuneji Suzuki *et al.***	)	Confirmation No. **7720**
Application No. **10/049,666**	)	Group Art Unit: **1612**
Filed: **February 15, 2002**	)	Examiner: **G. S. Kishore**
Title: **Pharmaceutical Agent Comprising a Benzamide Derivative as Active Ingredient**	)	Date: June 28, 2011

APPELLANTS' BRIEF UNDER 37 C.F.R. § 41.37

This brief is in furtherance of the Notice of Appeal filed in the above-identified patent application on March 28, 2011. A fee of $540.00 as required under 37 C.F.R. §41.20(b)(2) is being paid concurrently herewith. The period for filing this brief has been extended through June 28, 2011 by payment of a one-month extension of time.

1. Table of Contents

The Real Party in Interest.....page 2

Related Appeals and Interferences.....page 2

Status of Claims.....page 3

Status of Amendments.....page 3

Summary of Claimed Subject Matter.....page 4

Grounds of Rejection to be Reviewed on Appeal.....page 5

Argument.....page 5

Claims Appendix.....page 24

Evidence Appendix.....page 28

Related Proceedings Appendix.....page 29

2. The Real Party in Interest

The real party in interest in this appeal is Bayer Schering Pharma Aktiengesellschaft of Berlin, Germany.

3. Related Appeals and Interferences

Appellants are not aware of any other appeals or interferences that will directly affect, or be directly affected by, or have a bearing on the Board's decision in this appeal.

4. Status of Claims

The status of the claims is as follows upon filing of this Appeal Brief:

Claims cancelled: 1 to 43, 45, 49

Claims withdrawn from consideration but not cancelled: None

Claims pending: 44, 46, 47, 48

Claims objected to: None

Claims allowed: None

Claims rejected: 44, 46, 47, 48

The claims on appeal are 44, 46, 47, 48.

5. Status of Amendments

Appellants filed an Amendment under 37 C.F.R. § 1.114 on October 4, 2010 in which claims 44 and 46 were amended and claims 45 and 49 were cancelled. No further amendments of the claims were made during the prosecution of the subject application up to the filing of the Notice of Appeal on March 28, 2011. As such, Appellants submit that these claims are the currently pending claims of record. The claims listed in the claims appendix herein reflect the claim amendments of the aforementioned Amendment under 37 C.F.R. § 1.114.

6. Summary of Claimed Subject Matter

Aspects of Appellants' present invention relate generally to pharmaceutical formulations of a benzamide compound or its pharmaceutically acceptable salts. These claimed pharmaceutical formulations unexpectedly stabilize the benzamide compound against degradation. Appellants' invention, as summarized below, is described in detail at page 1, line 27 to page 3, line 2 of the specification with the unexpected results indicated, *inter alia*, in Tables 1-8.

In accordance with the embodiment of the invention that is independent claim 44, a pharmaceutical formulation of a benzamide compound of Formula (1) includes an excipient consisting of D-mannitol, a lubricant consisting of magnesium stearate, a disintegrant consisting of carboxymethylstarch sodium, and at least one member selected from an amino compound and an inorganic compound, wherein the amino compound is tris(hydroxymethyl)aminomethane and the inorganic base selected from the group consisting of sodium carbonate, potassium carbonate and potassium bicarbonate. Support for claim 44 may be found in Appellants' specification at, *inter alia*, page 3, line 3 to page 4, line 14; page 6, line 33 to page 7, line 10; page 7, lines 27-37; and page 8, lines 2-10.

In accordance with the embodiment of the invention that is independent claim 46, a pharmaceutical formulation of a benzamide compound of Formula (1)

includes at least one solvent that is a polyethylene glycol and at least one member selected from the recited groups of particular organic acid salts, amino compounds and inorganic bases. Support for claim 46 may be found in Appellants' specification at, *inter alia*, page 3, line 3 to page 4, line 22; page 6, line 33 to page 7, line 37 and page 16, Table 7.

7. Grounds of Rejection to be Reviewed on Appeal

Whether claims 44, 46, 47 and 48 are unpatentable under 35 U.S.C. § 103(a) as obvious over European Patent Application No. 0847 992 to Suzuki *et al.* ("Suzuki").

Whether claims 44, 46, 47 and 48 are unpatentable under 35 U.S.C. § 103(a) as obvious over Suzuki in view of U.S. Patent No. 5,681,584 to Savastano *et al.* ("Savastano") and further in view of any one of or all of U.S. Patent No. 7,041,313 to Dietrich ("Dietrich"), U.S. Patent No. 5,665,348 to Okayama ("Okayama") and U.S. Patent No. 5,962,454 to Ueda ("Ueda").

8. Argument

Appellants respectfully assert that the rejections under 35 U.S.C. §103(a) are improper and should be reversed.

A. Independent Claims 44 and 46

With respect to independent claim 44, Appellants respectfully assert that the applied art does not teach or suggest a combination of

a pharmaceutical formulation of a benzamide of Formula (I) or a pharmaceutically salt thereof;

an excipient consisting of D-mannitol;

a lubricant consisting of magnesium stearate;

a disintegrant consisting of carboxymethylstarch sodium; and

at least one member selected from the group consisting of an amino compound and an inorganic base,

wherein

the amino compound is tris(hydroxymethyl)aminomethane; and

the inorganic base is at least one member selected from the group consisting of sodium carbonate, potassium carbonate and potassium bicarbonate.

With respect to independent claim 46, Appellants respectfully assert that the applied art does not teach or suggest a combination of

a pharmaceutical formulation of a benzamide of Formula (I) or a pharmaceutically salt thereof;

at least one solvent that is a polyethylene glycol; and

at least one member selected from the group consisting of an organic acid salt, an amino compound and an inorganic base;

wherein

the organic acid salt is at least one member selected from the group consisting of monosodium fumarate, sodium alginate, sodium dehydroacetate, sodium erythorbate, and trisodium citrate;

the amino compound is at least one member selected from the group consisting of tris(hydroxymethyl)aminomethane, monoethanolamine, diethanolamine, triethanolamine, diisopropanolamine, triisopropanolamine, dihydroxyaluminum aminoacetate, arginine, creatinine, sodium glutamate, glycine, L-arginine L-glutamate, and carbachol; and

the inorganic base is at least one member selected from the group consisting of sodium carbonate, ammonium carbonate, sodium bicarbonate, potassium bicarbonate, disodium phosphate, and ammonia.

1. Rejection of Claims 44 and 46 under 35 U.S.C. 103(a) over Suzuki

The Office Action dated October 29, 2010 asserts that Suzuki teaches that Appellants' claimed benzamide derivative "may be prepared with generally used diluents or excipients, such as binders, extenders, fillers, moisturizers, disintegrants, surfactants, and lubricants" (pages 2-3 of the Office Action). It is

further asserted that Suzuki "teaches the use of lactose, calcium carbonate, amino acids, starch, methyl celluloses, calcium Carmellose, sugars, stearates, talc, polyethylene glycol, sodium alginate and many other well known excipients" (page 3 of the Office Action). Accordingly, the Office Action finds Appellants' claimed formulation obvious over Suzuki.

Appellants respectfully disagree with the obviousness rejection asserted by the Office Action. Suzuki does not teach or suggest pharmaceutical formulations comprising a benzamide compound of formula (1) in combination with the specific additives as claimed in independent claims 44 and 46. Instead, Suzuki merely provides a generalized and undifferentiated list of additives, such as those listed at page 46, which may potentially be used for pharmaceutical formulations of various types. For example, regarding a tablet formulation, Suzuki states the following:

> "For preparing tablets, a variety of carriers well-known in the art may be used. Such a carrier includes excipients such as lactose, glucose, starch, calcium carbonate, kaoline, crystalline cellulose and silicic acid; binders such as water, ethanol, propanol, simple syrup, glucose solution, starch solution, gelatin solution, carboxymethyl cellulose, shellac, methyl cellulose and polyvinyl pyrrolidone; disintegrators such as dried starch, sodium alginate, powdered agar,

> calcium carmelose, starch and lactose; disintegration retarders such as sucrose, cocoa butter and hydrogenated oil; absorption promoters such as quaternary ammonium base and sodium lauryl sulfate; moisturizing agents such as glycerin and starch; adsorbents such as starch, lactose, kaoline, bentonite, colloidal silicic acid; and glidants such as talc, stearates and polyethylene glycol." (page 46, lines 9-16 of Suzuki)

Without additional guidance, a person of ordinary skill in the art would have no rationale for choosing from between the distinct classes of compounds recited in the above listings of additives in Suzuki (*e.g.*, excipients, binders, disintegrators, absorption promoters, absorbents, glidants, *etc.*) – and even less from the particular compounds that are representative of each class – to arrive at the specific formulations claimed in Appellants' independent claim 44. These formulations of claim 44 are recited as a pharmaceutical formulation of a benzamide of Formula (I) or a pharmaceutically acceptable salt thereof in combination with a specific excipient that is D-mannitol; a specific lubricant that is magnesium stearate; a specific disintegrant that is carboxymethylstarch sodium; at least one of an amino compound and an inorganic base, wherein the amino compound is specifically

tris(hydroxymethyl)aminomethane and the inorganic base is selected from sodium carbonate, potassium carbonate and potassium bicarbonate. Clearly, Suzuki does not teach the specific formulations of Appellants' claim 44. The Examiner even acknowledges on page 3 of the Office Action dated October 29, 2010 that Suzuki "does not specifically teach mannitol, carboxymethyl starch and sodium carbonate". With this admission by the Examiner, it seems apparent that a person of ordinary skill would have no rationale for selecting a combination containing these particular species in the absence of an additional teaching.

Similarly, there would be no rationale for a person of ordinary skill in the art to prepare the particular formulations recited in claim 46 by Appellants with only the knowledge of the teaching of Suzuki. More specifically, a person of ordinary skill in the art would have no rationale for preparing a pharmaceutical formulation of a benzamide of Formula (I) or a pharmaceutically salt thereof in combination with at least one solvent that is polyethylene glycol; at least one of an organic acid salt selected from the group consisting of monosodium fumarate, sodium alginate, sodium dehydroacetate, sodium erythorbate, and trisodium citrate; at least one of an amino compound selected from the group consisting of tris(hydroxymethyl)aminomethane, monoethanolamine, diethanolamine, triethanolamine, diisopropanolamine, triisopropanolamine, dihydroxyaluminum

aminoacetate, arginine, creatinine, sodium glutamate, glycine, L-arginine, L-glutamate, and carbachol; and at least one of an inorganic base selected from the group consisting of sodium carbonate, ammonium carbonate, sodium bicarbonate, potassium bicarbonate, disodium phosphate, and ammonia.

Appellants' claimed formulations also have unexpected stabilizing properties associated with them. These unexpected properties are based on Appellants' observation that select benzamide compounds, while stable ***per se*** (*i.e.*, in the absence of various additives), may become unstable when present in a pharmaceutical formulation containing commonly used excipients and further, that some of these excipients actually accelerate the degradation of the benzamide compounds while other commonly used excipients do not. No one before Appellants has made these observations. Further, Appellants have exploited these findings by preparing and claiming pharmaceutical formulations that promote stabilization of these benzamide compounds.

As a representative example of these unexpected results, Table 1 is presented below as a sampling of the data originally shown in Table 4 at page 13 of Appellant's specification. This data resulted from the testing of tablets containing the compositions described in Tables 2 and 3 at page 12 of Appellants' specification – namely, the benzamide compound N-(2-aminophenyl)-4-[N-

(pyridine-3-yl)methoxycarbonyl]aminomethyl benzamide (compound 1) in combination with various additives.

Table 1. Total Amount (%) of Degradation of Tablets Containing Compound 1 (1.0 mg) + Additives

Tablet #	Additives	60°C air-tight for 4 weeks (FN8)	80°C air-tight for 3 days (FN8)
a	60.0 mg of D-mannitol + 3.3 mg of carboxymethyl starch sodium + 0.7 mg of magnesium stearate (FN1)	1.0	1.3
b	60.0 mg of D-mannitol + 3.3 mg of carboxymethyl starch sodium + 0.7 mg of magnesium stearate + 0.5 mg of tris(hydroxymethyl)aminomethane (FN2)	0.7	0.5
c	60.0 mg of D-mannitol + 3.3 mg of carboxymethyl starch sodium + 0.7 mg of magnesium stearate + 0.5 mg of potassium bicarbonate (FN3)	--	0.4
d	60.0 mg of D-mannitol + 3.3 mg of carboxymethyl starch sodium + 0.7 mg of magnesium stearate + 0.5 mg of sodium carbonate (FN4)	--	0.4
	40.6 mg of D-mannitol + 17.4 mg of		

e	partially gelatinized starch + 2.0 mg of hydroxypropyl cellulose + 3.3 mg of carmellose calcium + 0.7 mg of magnesium stearate (FN5)	4.1	3.0
f	40.6 mg of D-mannitol + 17.4 mg of partially gelatinized starch + 2.0 mg of hydroxypropyl cellulose + 0.7 mg of magnesium stearate (FN6)	4.5	2.1
g	40.6 mg of D-mannitol + 17.4 mg of partially gelatinized starch + 2.0 mg of polyvinylpyrrolidone + 3.3 mg of carmellose calcium + 0.7 mg of magnesium stearate (FN7)	5.8	5.3

(FN1): Same as sample "b" in Table 2 in Appellants' specification at page 12

(FN2): Same as sample "c" in Table 2 in Appellants' specification at page 12

(FN3): Same as sample "d" in Table 2 in Appellants' specification at page 12

(FN4): Same as sample "e" in Table 2 in Appellants' specification at page 12

(FN5): Same as sample "g" in Table 3 in Appellants' specification at page 12

(FN6): Same as sample "h" in Table 3 in Appellants' specification at page 12

(FN7): Same as sample "i" in Table 3 in Appellants' specification at page 12

(FN8): Data appears in Table 4 in Appellants' specification at page 13

As shown above in Table 1, formulations encompassed by claim 44 (samples b, c and d) exhibit superior properties with respect to the stability of a

tested benzamide compound against degradation compared to samples a, e, f, and g, each of which represents a formulation that is not encompassed by claim 44. In comparing the stability data among samples a to g, it is clear that samples b, c and d exhibit superior stability against degradation under both of the storage conditions tested (*i.e.,* 60° C air-tight/4 weeks and 80° C air-tight/3 days) compared to samples a, e, f, and g. For example, under conditions of 80° C air-tight/3 days, samples b, c and d show 0.5%, 0.4% and 0.4% degradation products, respectively, while in contrast, samples a, e, f and g show 1.3%, 3.0%, 2.1% and 5.3% degradation products, respectively. Although all samples contain (i) the benzamide compound, (ii) D-mannitol as an excipient, (iii) magnesium stearate as a lubricant and (iv) carboxymethylstarch sodium or partially gelatinized starch as a disintegrant, the samples b, c and d additionally contain an amino compound and/or an inorganic base as required by claim 44.

In contrast, samples outside the scope of claim 44 (*i.e.*, a, e, f and g) do <u>not</u> contain an additional amino compound or inorganic base. For this reason, samples a, e, f and g are less stable than the samples b, c and d in that they result in a higher percentage of degradation products. Table 1 therefore clearly demonstrates the advantage that Appellants' claimed invention provides with respect to the prior art. The previously submitted declaration of Masahiro Sakabe under 37 C.F.R. 1.132

(submitted herein as Exhibit A) attests to the statistical significance of the differences between the numbers appearing in the tables (such as, *e.g.*, Tables 2 and 3 of Appellants' specification).

The prior art, and in particular Suzuki, does not contain any information that would teach or suggest the fact that otherwise stable benzamide compounds may become unstable in pharmaceutical formulations or that would allow a person of ordinary skill in the art to differentiate between the desired (stabilizing) formulations represented by samples b, c and d of Table 1 above versus the undesired (non-stabilizing) formulations represented by samples a, e, f and g. More fundamentally, Suzuki does not contemplate the problem of degradation of the benzamide compound (noted by Appellants) at any point in its disclosure. Clearly then, Suzuki cannot provide any suggestion to a person of ordinary skill in the art as to how the problem of benzamide degradation may be solved if there is no recognition of the problem. Accordingly, Appellants submit that the knowledge of how to prepare stabilizing formulations containing these benzamide compounds, as claimed in Appellants' claim 44, could not have been derived from Suzuki.

The Office Action asserts that "choosing the appropriate compounds falling under each category with a reasonable expectation of success would have been obvious to one of ordinary skill in the art at the time the invention was made"

(page 3 of the Office Action). Appellants respectfully disagree and submit that in the absence of any appreciation or awareness in Suzuki of the destabilizing effects of common excipients on the benzamide compounds of Appellants' claim 44, a person of ordinary skill in the art would have no mechanism for selecting particular excipients over others that might otherwise appear suitable in preparing the benzamide formulations of Appellants' claim 44.

Table 2 below (shown originally with additional examples as Table 6 in Appellants' specification at page 15) relates to pharmaceutical formulations as encompassed by Appellants' independent claim 46 (*i.e.*, liquid formulations). More specifically, Table 2 is a representative example of the degree of degradation of liquid formulations of 20 mg/mL of the benzamide compound N-(2-aminophenyl)-4-[N-(pyridine-3-yl)methoxycarbonyl]aminomethyl benzamide (compound 1) in polyethylene glycol 400 containing an additive at a concentration of 0.05 M.

Table 2. % Degradation of liquid formulations of 20 mg/mL of compound 1 in polyethylene glycol 400 containing an additive at a concentration of 0.05M

Additive	80°C air-tight for 3 days
none	41.4

sodium fumarate	21.6
tris(hydroxymethyl)aminomethane	2.9
diethanolamine	3.9
ammonium carbonate	3.6
potassium bicarbonate	15.5

As can be seen from the data in Table 2 above, a polyethylene glycol solution of benzamide compound 1 results in extensive degradation (*i.e.*, 41.4%) of the benzamide compound. However, the addition of an organic acid salt (*e.g.*, sodium fumarate), an amino compound (*e.g.*, tris(hydroxymethyl)aminomethane or diethanolamine) or an inorganic base (*e.g.*, ammonium carbonate or potassium bicarbonate) greatly increases the stability of these solutions, as evidenced by a lower percentage of degradation products as compared to the control sample. Thus, liquid formulations of benzamide compounds as claimed in Appellants' claim 46 are superior to previously known formulations with respect to their stability against degradation. As discussed above, Suzuki does not contemplate the problem of degradation of benzamide compounds in pharmaceutical formulations, even less being able to instruct a person of ordinary skill in the art as to how this problem could be addressed. In contrast to Appellants' claim 46, Suzuki does not

teach or suggest that, in addition to a solvent, an organic acid salt, an amino compound and/or an inorganic base is required to stabilize the benzamide compound. Suzuki separately lists polyethylene glycol (page 46, line 16 of the description), sodium alginate (page 46, line 12 of the description) and calcium carbonate (page 46, line 10 of the description) as suitable excipients for the preparation of tablets. However, the list in which these excipients appear in Suzuki is large and includes many other agents. Appellants submit that because Suzuki does not suggest the combination of the particular components recited in Appellants' claim 46, Suzuki clearly does not appreciate Appellants' discovery that these particular additives stabilize formulations of benzamide compounds containing polyethylene glycol at least one member selected from the group consisting of an organic acid salt, an amino compound and an inorganic base; wherein

the organic acid salt is at least one member selected from the group consisting of monosodium fumarate, sodium alginate, sodium dehydroacetate, sodium erythorbate, and trisodium citrate;

the amino compound is at least one member selected from the group consisting of tris(hydroxymethyl)aminomethane, monoethanolamine, diethanolamine, triethanolamine, diisopropanolamine, triisopropanolamine,

dihydroxyaluminum aminoacetate, arginine, creatinine, sodium glutamate, glycine, L-arginine L-glutamate, and carbachol; and

the inorganic base is at least one member selected from the group consisting of sodium carbonate, ammonium carbonate, sodium bicarbonate, potassium bicarbonate, disodium phosphate, and ammonia.

. Therefore, the increased stability of the pharmaceutical formulations according to Appellants' claim 46 could not have been expected by a person of ordinary skill in the art based on the teaching of Suzuki.

2. Rejection under 35 U.S.C. 103(a) over Suzuki in view of Savastano and further in view of any one of or all of Dietrich, Okayama and Ueda

In finding Appellants' claimed formulation obvious over Suzuki in view of Savastano and further in view of any one of or all of Dietrich, Okayama and Ueda, the Office Action dated October 29, 2010 relies on Savastano for teaching selected components that the Office Action acknowledges are not taught by Suzuki (such as mannitol, carboxymethyl starch and sodium carbonate). In particular, the Office Action appears, on pages 3-5, to indicate that while Savastano does not explicitly disclose each of the components that are missing from the disclosure of Suzuki, Savastano does teach equivalents of these components that are recognized as such

by Dietrich, Okayama and Ueda. For example, the Office Action states that although "Savastano does not teach the use of carboxymethyl starch, one of ordinary skill in the art would be motivated to use this compounds instead of carboxymethylcellulose [as taught by Savastano] because of the equivalency between these compounds as taught by Okayama and Ueda" (page 4 of the Office Action).

Appellants respectfully disagree with this asserted rejection. Similar to Suzuki, Savastano contains undifferentiated lists of excipients. While Appellants acknowledge that Savastano lists mannitol as a suitable additive, Savastano also lists lactose as an equally suitable additive in the same sentence. As observed by Appellants and as shown in Table 1 at page 11 of Appellants' specification, lactose hastens degradation of a benzamide compound encompassed by Appellants' claims 44 and 46. By not distinguishing between a suitable excipient and a non-suitable excipient, Savastano cannot be relied upon to address the clear inadequacies present in Suzuki regarding the awareness of the destabilizing effects of various additives on benzamide compounds or the particular component requirements recited by Appellants' claims 44 and 46. The secondary references of Dietrich, Okayama and Ueda cannot remedy the above-noted deficiencies that are present in both Suzuki and Savastano. Identification of equivalent components by Dietrich,

Okayama and/or Ueda, without an awareness or contemplation of the problem to be addressed – *i.e.*, the degradation of benzamide compounds in pharmaceutical formulations, does nothing to provide a rationale for selecting some components over other components in constructing the formulations recited in Appellants' claims 44 and 46.

Given the complete lack of recognition by Suzuki, Savastano, Dietrich, Okayama and Ueda of the destabilizing effects of various common excipients typically used in pharmaceutical formulations on the benzamide compounds recited in Appellants' claims 44 and 46, it appears that the Office Action is engaging in impermissible hindsight when asserting the obviousness of Appellants' claimed formulations.

Appellants submit that the "obvious to try" test as defined in KSR Int'l Co. v. Teleflex Inc., 127 S.Ct. 1727 (2007) ("KSR") has not been satisfied because of the lack of identified, predictable solutions. The Supreme Court in KSR has indicated that obviousness exists where the solutions are predictable and where a person of ordinary skill would have good reason to pursue the known options. That is not the case here, where it is not apparent from a simple listing of a large number of excipients, which ones individually or in combination would destabilize the benzamide compounds recited in Appellants' claims 44 and 46.

For at least the above stated reasons, Appellants respectfully submit that the subject matter recited by independent claims 44 and 46 is both novel and nonobvious over the teachings of Suzuki alone or in combination with Savastano and any or all of Dietrich, Okayama and/or Ueda. Accordingly, Appellants respectfully submit that the rejections under 35 U.S.C. 103(a) of independent claims 44 and 46 are improper and should be reversed.

B. Dependent Claims 47 and 48

Appellants respectfully assert that dependent claims 47 and 48 are individually allowable at least because of their respective dependencies from independent claim 47 and for the reasons set forth above. Thus, the rejection of dependent claims 47 and 48 are improper and should be reversed.

Suzuki, either alone or in view of Savastano and further in view of any or all of Dietrich, Okayama and/or Ueda, does not teach or suggest claim 47, which depends from claim 46 and further limits the composition to polyethylene glycol 400 as the at least one solvent; and a pH in the range of about 7 to about 11 through the addition of an acid or base.

Suzuki, either alone or in view of Savastano and further in view of any or all of Dietrich, Okayama and/or Ueda, does not teach or suggest claim 48, which

depends from claim 46 and further limits the composition to hydrochloric acid as the acid and sodium hydroxide as the base.

In view of the foregoing, Appellants respectfully request the reversal of the Examiner's rejections and the allowance of the pending claims. If there are any other fees due in connection with the filing of this Appellants' Brief, please charge the fees to our Deposit Account No. 50-0310.

If a fee is required for an extension of time under 37 C.F.R. §1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account No. 50-0310.

Respectfully submitted,

MORGAN LEWIS & BOCKIUS LLP

Dated: **June 28, 2011**

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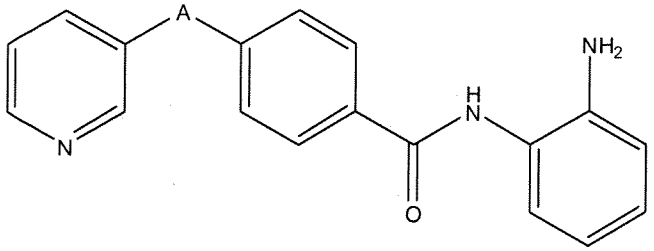
9. Claims Appendix

Subsequent to entry of the Amendment and Response under 37 C.F.R. § 1.114, the claims read as follows:

Claims 1-43 (cancelled).

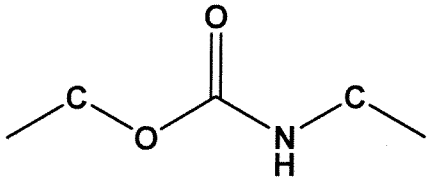
Claim 44 (rejected): A pharmaceutical formulation comprising:

a benzamide derivative represented by formula (1):



(1)

wherein A represents a structure shown by formula (2):



(2)

or a pharmaceutically acceptable salt thereof;

an excipient consisting of D-mannitol;

a lubricant consisting of magnesium stearate;

a disintegrant consisting of carboxymethylstarch sodium; and

at least one member selected from the group consisting of an amino compound and an inorganic base,

wherein

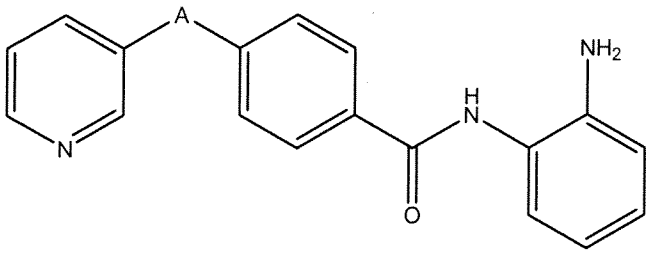
the amino compound is tris(hydroxymethyl)aminomethane; and

the inorganic base is at least one member selected from the group consisting of sodium carbonate, potassium carbonate and potassium bicarbonate.

Claim 45 (cancelled)

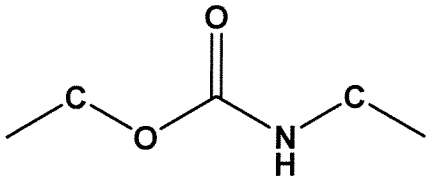
Claim 46 (rejected): A pharmaceutical formulation comprising:

a benzamide derivative represented by formula (1):



(1)

wherein A represents a structure shown by formula (2):



(2)

or a pharmaceutically acceptable salt thereof;

at least one solvent that is a polyethylene glycol; and

at least one member selected from the group consisting of an organic acid salt, an amino compound and an inorganic base;

wherein

the organic acid salt is at least one member selected from the group consisting of monosodium fumarate, sodium alginate, sodium dehydroacetate, sodium erythorbate, and trisodium citrate;

the amino compound is at least one member selected from the group consisting of tris(hydroxymethyl)aminomethane, monoethanolamine, diethanolamine, triethanolamine, diisopropanolamine, triisopropanolamine, dihydroxyaluminum aminoacetate, arginine, creatinine, sodium glutamate, glycine, L-arginine L-glutamate, and carbachol; and

the inorganic base is at least one member selected from the group consisting of sodium carbonate, ammonium carbonate, sodium bicarbonate, potassium bicarbonate, disodium phosphate, and ammonia.

Claim 47 (rejected): The pharmaceutical formulation according to claim 46 wherein

the at least one solvent is polyethylene glycol 400; and

the formulation is maintained at a pH in the range of about 7 to about 11 through addition of an acid or a base.

Claim 48 (rejected): The pharmaceutical formulation according to claim 47 wherein the acid is hydrochloric acid and the base is sodium hydroxide.

Claim 49 (cancelled)

10. Evidence Appendix

Attached as Exhibit A is an inventor declaration under 37 C.F.R. 1.132 by Mr. Masahiro Sakabe, attesting to the significance of the observed data. This declaration was previously submitted to the U.S. Patent Office in a response filed on December 4, 2006 and was entered into the prosecution record as evidenced by the examiner's comments in the Office Action dated January 9, 2007.

11. Related Proceedings Appendix

No information is appended under this section.

EXHIBIT A

PATENT
Attorney Docket No. 054160-5060

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Tsuneji Suzuki *et al.*	)	
U.S. Application No. 10/049,666	)	Group Art Unit: 1615
Filed: February 15, 2002	)	Examiner: Gollamudi S. Kishore
Title: **Pharmaceutical Agent Comprising a Benzamide Derivative as Active Agent**	)	Date: December 4, 2006

Commissioner for Patents
U.S. Patent and Trademark Office
Customer Service Window, Mail Stop Amendment
Randolph Building
401 Dulany Street
Alexandria, VA 22314

DECLARATION UNDER 37 C.F.R. § 1.132

I, the undersigned, Masahiro Sakabe, do hereby declare that:

1. I am a citizen of Japan, residing at 3-8-6-804, Kikukawa Sumida-ku, Tokyo, Japan.

2. I have been awarded a Bachelor's degree in chemistry from the Chiba University.

3. I have been employed by Nihon Schering K. K. since January 1st, 2001 and I am presently a Manager at Nihon Schering K. K.. During my employment at Nihon Schering K. K., I have been engaged in research & development in the area of Pharmaceutics and in-vitro diagnostics.

4. I am familiar with the specification and pending claims of U.S. Patent Application No. 10/049,666. I have reviewed the Office Action dated March 2, 2006 and the Interview Summary dated May 18, 2006. Regarding the data presented in the tables in the specification, I

believe that as an artisan skilled in the art of high-performance liquid chromatography (HPLC), the differences between the listed numbers are statistically significant. For example, Table 1 shows that when D-mannitol and compound 1 are mixed together and subjected to the indicated conditions, compound 1 is degraded by 0.21 percent (%) relative to the total amount of compound 1 present in the mixture. This value is comparable to the stability of compound 1 in the absence of any additional component (0.18 or 0.19 depending on the conditions tested). In contrast, when lactose and compound 1 are mixed together and subjected to the indicated conditions, compound 1 is degraded by 0.55 percent (%) or 0.44 % relative to the total amount of compound 1 present in the mixture, depending on the particular conditions tested. Given my level of skill in HPLC chromatography, I believe that the difference between, for example, 0.21 (D-mannitol + compound 1) and 0.55 or 0.44 (lactose + compound 1) is statistically significant in that a conclusion may be drawn regarding the stabilizing effects of D-mannitol on compound 1 and the destabilizing effects of lactose on compound 1.

5. I further declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true, and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: November 16, 2006 By: Masahiro Sakabe

(Masahiro Sakabe)